Focus this GM: Radical chemistry of sugars (especially at the anomeric carbon) to synthesize C-nucleosides.

**Some N and C-nucleosides**


**Some Features of C-Nucleosides**
- The C-C bond is much less resistant to chemical and enzymatic degradation.
- C-glycosides are stable pharmacophores and yield novel enzyme inhibitors.
- More conformationally stable - no anomeric effect
- Effective HIV, anti-viral, and anti-bacterial treatments

**Some Other Nucleoside Classes:**

Carbocyclic nucleosides (**carbanucleosides**):
- CH$_2$ prevents chemical and the enzymatic hydrolytic cleavage of the glycosidic bond
- CH$_2$ imparts lipophilicity - a benefit for oral uptake penetration

Fluorinated nucleosides:
- Small steric size, high electronegativity, carbon-fluorine bond sensitivity.
- Positive effect on drug clearance and metabolism

*3,4,and 6 membered rings not shown*
Axially orientated anomic radicals.

\[
\begin{align*}
\text{OH}(\text{CH}_2\text{O})_n\text{H}, & \quad \text{K}_2\text{CO}_3, \text{MeOH} \\
& \quad \text{rt, 3h} \\
& \quad \text{pyr./Ac}_2\text{O (2:1)} \\
& \quad 0^\circ\text{C}
\end{align*}
\]

\[
\begin{align*}
\text{BnO} & \quad \text{OAc} \\
\text{BnO} & \quad \text{BnO} \\
\text{BnO} & \quad \text{NO}_2 \\
\text{BnO} & \quad \text{BnO}
\end{align*}
\]

3-5 steps

\[
\alpha : \beta = 85 : 15
\]

\[
\begin{align*}
\text{BnO} & \quad \text{OAc} \\
\text{BnO} & \quad \text{BnO} \\
\text{BnO} & \quad \text{NO}_2 \\
\text{BnO} & \quad \text{BnO}
\end{align*}
\]

n-Bu\textsubscript{3}SnH, AIBN (dropwise 1-2h) Benzene, \Delta

only observed product

Separate and Subject:

\[
\begin{align*}
\text{BnO} & \quad \text{OAc} \\
\text{BnO} & \quad \text{BnO} \\
\text{BnO} & \quad \text{NO}_2 \\
\text{BnO} & \quad \text{BnO}
\end{align*}
\]

n-Bu\textsubscript{3}SnH, AIBN

same result: only observed product

FMO Theory: stabilizing effect is due to interaction of the SOMO with the LUMO of the neighboring C-O bond.

*conclusion - glycosyl radicals prefer an axial anomic configuration

What about the O atom?

\[
\begin{align*}
\text{BnO} & \quad \text{OAc} \\
\text{BnO} & \quad \text{BnO} \\
\text{BnO} & \quad \text{NO}_2 \\
\text{BnO} & \quad \text{BnO}
\end{align*}
\]

87

change in selectivity

But For 5 Membered furanoses - Sterics and stereoelectronics play a role

\[
\begin{align*}
\text{TrO} & \quad \text{OAc} \\
\text{O} & \quad \text{O}
\end{align*}
\]

90%

\[
\begin{align*}
\text{TrO} & \quad \text{OAc} \\
\text{O} & \quad \text{O}
\end{align*}
\]

87%

*Both do not give same result as in pyranose
Anomeric Radical(s) (Some Effects)

Radical C-Glycosidations with Nitroglycosides

\[
\begin{align*}
\text{NO}_2 & \quad \text{CN} \\
\text{Bu}_3\text{SnH} & \quad 55\% \\
\end{align*}
\]

\[
\begin{align*}
\text{CN} & \quad \text{CN} \\
\text{Bu}_3\text{SnH} & \quad \text{AIBN} \\
45\% & \\
\end{align*}
\]

Conditions
Photochemical
\[\text{Yield (\%) } \alpha:\beta \]
\[
\begin{align*}
\text{cat. } \text{Bu}_3\text{SnOTf} & \quad 87 \\
\text{95} & \quad 1:99 \\
\end{align*}
\]

Stereochemical result based upon method of radical generation.
- photochemical favors \(\alpha\) anomer while chemical methods favors \(\beta\)

Radical C-Glycosidations with Glycosidic Methylthiocarbonates

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{Bz} & \quad \text{Bz} \\
\text{Bu}_3\text{SnH}, \text{AIBN} & \quad 62\% \\
\text{SM} & \quad 2\% \\
\end{align*}
\]

- No stereochemical preference

Stereochemistry of A and B dependent on PG Used

A.

\[
\begin{align*}
\text{AcO} & \quad \text{OAc} \\
\text{BnO} & \quad \text{BnO} \\
\text{Br} & \quad \text{Br} \\
\text{AIBN} & \quad \beta:\alpha = >20:1 \\
\text{93}\% & \\
\end{align*}
\]

B.

- flipping after deprotection

\[
\begin{align*}
\text{AcO} & \quad \text{OAc} \\
\text{BnO} & \quad \text{BnO} \\
\text{PGN} & \quad \\
\text{AIBN} & \quad \text{then deprotection and BzCl, DMAP} \\
\alpha:\beta = 1:99 & \quad 61\% \\
\end{align*}
\]

For furanose - stereochemistry dependent upon R

R

\[
\begin{align*}
\text{Conditions} & \quad \text{Yield(\%) } \alpha:\beta \\
\text{Photochemical} & \quad \text{complex mixture} \\
\text{cat. } \text{Bu}_3\text{SnOTf} & \quad 80 \\
79 & \quad 1:99 \\
91 & \quad 40:60 \\
\end{align*}
\]

**Addition to Heterocycles - (Methods-1)**

**General Scheme:**

![Chemical Reaction Scheme]

**Proposed Mechanism:**

1. **RCOOH, ArI, X₂ (hν or Δ)**
2. **Ar = C₆H₅, C₆F₅**
3. **X = CF₃CO₂**
4. **R = alkyl, acyl, and ribofuranosyl**

**Order of Reactivity:**

- Primary < Secondary < Tertiary

**Other Observations**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BnO</td>
<td></td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>OBOB</td>
<td>Δ</td>
<td></td>
<td>78</td>
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</tbody>
</table>

*Reactions highly dependent on conditions*

**Conditions:** DCM/quartz cell/Argon/low pressure mercury lamp 0°C-r.t.
Addition to Heterocycles (Methods - 2)

General Scheme:

with nucleoside sugars:

\[
\begin{align*}
\text{BnO} & \quad \text{O} & \quad \text{OH} & \quad \text{BnO} & \quad \text{O} & \quad \text{O} & \quad \text{BnO} & \quad \text{BnO} \\
\text{45\% (\alpha:\beta = 20:80)} & \quad \text{H}_2 & \quad \text{PdO} & \quad \text{cyclohexane} & \quad \text{H}_2 & \quad \text{PdO} & \quad \text{cyclohexane}
\end{align*}
\]

from 2 tetrahydrofurfuryl carboxylic acid:

\[
\begin{align*}
\text{H}_2 & \quad \text{COOC} & \quad \text{Br} & \quad \text{H}_2 & \quad \text{COOC} & \quad \text{Br} & \quad \text{Br} & \quad \text{Br} & \quad \text{N}
\end{align*}
\]

Mechanism (Part I):

Mechanism (Part II):


Experiments with Acrylonitrile to determine general PG effects:

\[ \text{attack at } \beta \text{ face only} \]

(\(\beta: \alpha = 73:27\))

*more shielding by the dioxolane ring than alkyl at C-4

\[ \text{attack at } \alpha \text{ face only} \]

(\(\beta: \alpha = 50:50\))

Conformations of triacetylxylosyl system (observed in ESR spectrum)

- \(\alpha\) products favored
- \(\beta\) products favored
- \(\beta\) products favored

Thus, \(\beta\) products are favored overall.

General Scheme:

\[ \text{(PhCOO)}_2 \]

(1.5-2 eq.)

\[ \text{TFA (2 eq.)} \]

\[ \text{PhH, } \Delta \]

(1 eq.)

\[ \text{X=I or CH}_2\text{I} \]

(1-3 eq.)

\[ \text{het} \]

\[ \text{NH} \]

89% (ratio N/A)

11%

"steric hindrance is clearly not determining factor as A adds to the most hindered position on the heteroaromatic ring"

C-8?

\[ \text{not observed} \]

but

\[ \text{no rxn} \]

Conclusions:

- Reactivity is dependent on cyclic structure.
- \(\alpha\)'s withdrawing and field effects by 5 O atoms reduce nucleophilic character of A & B
- Effect of O atoms (2 atoms in \(\beta\) position for A vs. 1 for B)
  - effect is greater for A.
  - \(\alpha\) considered electrophilic.
Addition to Heterocycles (selectivity- 2)

<table>
<thead>
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<th>Heterocycle</th>
<th>Product</th>
<th>Yield (%)</th>
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<tbody>
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<td>25</td>
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<td><img src="image7" alt="Heterocycle" /></td>
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</tr>
<tr>
<td><img src="image9" alt="Heterocycle" /></td>
<td><img src="image10" alt="Product" /></td>
<td>27%</td>
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</tbody>
</table>

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<thead>
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<th>Heterocycle</th>
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</thead>
<tbody>
<tr>
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<td><img src="image16" alt="Product" /></td>
<td>22</td>
</tr>
</tbody>
</table>

*Protecting Groups control facial selectivity.
**Methods to generate radicals at anomeric carbon:**

- a) Bu$_3$SnH (Hg-h$_v$ or $\Delta$)
  \[ \text{X} = \text{NO}_2, \text{I}, \text{Br}, \text{Cl}, \text{SeAr}, \text{SAr} \]
- b) Bu$_3$SnSnBu$_3$ (Hg-h$_v$)
  \[ \text{X} = \text{NO}_2, \text{I}, \text{Br}, \text{Cl}, \text{SeAr}, \text{SAr} \]
- c) (C$_2$H$_5$)$_3$B (air) or N-acetoxy-2-thiopyridone (W-h$_v$)
  \[ \text{X} = \text{TeAr} \]
- d) Ester of N-Hydroxy-2-thiopyridone (W-h$_v$)
  \[ \text{X} = \text{COOH} \]
- e) (Diacyloxyiodo)arenes (Hg-h$_v$ or $\Delta$)
- f) Hg-h$_v$
  \[ \text{X} = \text{COBu-t etc} \]
- g) W-h$_v$
  \[ \text{X} = \text{Co(dmgH)$_2$Py} \]

*All of these methods require the use of tin and/or photochemical conditions. Most require reflux in benzene or acetonitrile.

**Nature of the radical(s):**

**Pyranosyl ring**

- axial $\sigma$ radical
- more nucleophilic
- equatorial $\sigma$ radical
- (more nucleophilic (axial) $\sigma$ radical)

**Furanosyl ring**

- axial $\sigma$ radical
- more nucleophilic
- equatorial $\sigma$ radical

**Some side reactions:**

1) The anomeric radical can be used to rearrange neighboring groups to the anomeric carbon.

2) Arylation by solvent

*Usually anomer radicals are more nucleophilic than carboxylic radicals due to interactions with the non-bonding electron pair on the ring O atom. Thus, the axial $\sigma$–radical is more stable and more nucleophilic than the corresponding equatorial $\sigma$–radical.

*The anomeric radical interacts by its high lying SOMO with the LUMO of an electron-poor alkene or electron poor aromatics.*